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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/556,803
Filing Date: November 14, 2005
Appellant(s): ARPAIA ET AL.

Daniel J. Pereira
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12/07/2010 appealing from the Office action mailed 08/06/2010.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application: Claims 15-17.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the

subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

2002/0165146 Hoffman et al. 11-2002

Katakam, M., et al. "Use of Poloxamer Polymers to Stabilize Recombinant Human Growth Hormane against Various Processing Stresses, Pharmaceutical Development and Technology, vol. 2, no. 2 (1997), pp. 143-149

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. **Claims 15 -17** are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoffman et al. (US 2002/0165146) (Hoffman) in view of Katakam et al. (Pharmaceutical Development and Technology, 1997) (Katakam).

In regard to claim 15, Hoffman teaches a method of chromatographic analysis of follicle stimulating hormone (FSH) protein in a sample for quantifying the total FSH protein. The method comprises:

performing chromatography on the protein sample (see paragraph [0083]); and

manipulating data to determine the quantity of the total FSH protein (see paragraph [0083]).

Hoffman teaches that pharmaceutically acceptable solubilizers such as, Pluronic F68 or poloxamer 188 may optionally be added to FSH solution to reduce aggregation

(see paragraph [0100]). Using ultra pure water as solvent for surfactant solution is a common practice in the art. At time of the invention it would have been obvious to one of ordinary skill in the art to prepare the protein sample by adding poloxamer 188 in ultra pure water to the sample in order to reduce aggregation during chromatography purification.

Hoffman does not specifically teach the concentration of Poloxamer 188 being 100 µg/ml. However, Katakam teaches that "surfactants (poloxamer) adsorb preferentially at the air/water interface. They are believed to minimize aggregation by reducing the adsorption of protein at the interface" (see page 145, right col. last paragraph). Katakam teaches that surfactant forms a complete monolayer at the surface of protein at its critical micelle concentration (cmc), the protection is expected to be linked to the cmc value (see page 146, left col. 1st paragraph). Here, Katakam teaches that the protection is a result of surfactant forms a monolayer on the surface of the protein. The mechanism is universal to all proteins. Katakam cites Thurow et al. that poloxamers prevent both the adsorption of dissolved proteins to hydrophobic interfaces and the resultant aggregation (see page 146, left col. 1st paragraph). According to Katakam, the critical micelle concentration (cmc) of poloxamer 188 (Pluronic F68) is 55 µg/ml (0.0055 g/dl) (see Table 1). The limitation of "100 µg/ml of poloxamer" recited in the instant claim is about twice of cmc (55 µg/ml) needed for the surfactant to form a complete monolayer on the surface of micelle as taught by Katakam. Therefore, at the time of the invention it would have been obvious for a routineer to try 100 µg/ml of Poloxamer 188 first, because Katakam teaches that more than 55 µg/ml (cmc concentration) is needed in order for poloxamer 188 to form a monolayer protection on the hydrophobic surface of a protein and it would save money and cause no harm to protein by trying lower concentration (twice amount of CMC) of surfactant first.

Hoffman does not specifically teach using data from calibration with a standard to calculate the quantity of the protein. However, using data from calibration with a standard to calculate the quantity of the protein is well known in the art. At time of the invention, it would have been obvious for a person of ordinary skill in the art to use data from calibration with a standard to calculate the quantity of the protein.

In regard to claim 16, simple dilution of protein sample to a level acceptable for the chromatographic system is well-known in the art.

In regard to claim 17, Hoffman teaches using size-exclusion chromatography to purify FSH (see paragraph [0083]).

(10) Response to Argument

II.

Appellant alleges that "The Examiner finds that Hoffman teaches manipulating data (see the Action at page 3, 3rd paragraph) in paragraph [0083] but Hoffman does not actually do so. Indeed, the Examiner contradicts himself on page 4, 2nd to last paragraph where he admits that Hoffman does not. This is the first reversible error." (Brief, page 5). Examiner respectfully disagrees. In the last Office action, page 4, 2nd to last paragraph, examiner stated: "Hoffman does not specifically teach using data from **calibration with a standard** to calculate the quantity of the protein. However, using data from calibration with a standard to calculate the quantity of the protein is well known in the art. At time of the invention, it would have been obvious for a person of ordinary skill in the art to use data from calibration with a standard to calculate the quantity of the protein". Thus, Examiner state that what Hoffman does not teach is "**calibration with a standard**", which is well known in the art.

In response to appellant argument that "the disclosure of surfactants is meant for the formulation of the purified protein not a suggestion to use such additives during chromatography" (Brief, page 6), Hoffman teaches performing chromatography on the FSH sample (see paragraph [0083]), and adding pharmaceutically acceptable solubilizers such as, Pluronic F68 or poloxamer 188 to FSH solution to reduce aggregation (see paragraph [0100]). At time of the invention it would have been obvious to one of ordinary skill in the art to use such additives during chromatography in order to reduce the aggregation of FSH.

In response to appellant argument that "Katakam does not describe FSH (the subject matter of the claimed invention and that of Hoffman) but only HGH (human

growth hormone) and there are no teachings in Katakam that allow one to envision the effects of Poloxamer surfactants on FSH in Hoffman" (brief, page 6), Katakam teaches that "surfactants (poloxamer) adsorb preferentially at the air/water interface, they are believed to minimize aggregation by reducing the adsorption of protein at the interface" (see page 145, right col. last paragraph). Katakam teaches that surfactant forms a complete monolayer at the surface of protein at its critical micelle concentration (cmc), the protection is expected to be linked to the cmc value (see page 146, left col. 1st paragraph). Here, Katakam teaches that the protection is a result of surfactant forms a monolayer on the surface of the protein. The mechanism is universal to all proteins.

Appellant argues that "While it is true that Katakam discusses effects of HGH aggregation in the presence of poloxamer, there are no teachings in this combination of art that even remotely suggests any problems with FSH" (Brief, page 7). In response, as has been discussed above, Katakam teaches that the protection is a result of surfactant forms a monolayer on the surface of the protein. The mechanism is universal to all proteins.

In response to appellant argument that "the concentration of Poloxamer 188 recited in Claim 15 (0.01%) is much closer to the "non-working" concentration of Poloxamer 188 (0.0055%), according to Katakam et al., than to the "working" concentration (0.2'%)." (Brief, page 10), Katakam teaches that surfactant forms a complete monolayer at the surface of protein at its critical micelle concentration (cmc), the protection is expected to be linked to the cmc value (see page 146, left col. 1st paragraph). According to Katakam, the critical micelle concentration (cmc) of poloxamer 188 (Pluronic F68) is 55 µg/ml (0.0055 g/dl) (see Table 1). The limitation of "100 µg/ml of poloxamer" recited in the instant claim is about twice of cmc (55 µg/ml) needed for the surfactant to form a complete monolayer on the surface of micelle as taught by Katakam. Thus, there is no reason for an ordinary skill in the art to believe that twice of cmc concentration of poloxamer 188 would not protect a protein from aggregation, because the 100 µg/ml is more than enough (about twice amount of 55 µg/ml needed) to form a monolayer micelle. The "working" condition of 0.2% in Katakam is a high end point that is still working in Katakam.

Appellant argues that "While the amount of poloxamer in the claims is twice the cmc reported in Katakam, the Examiner's conclusion that generally Katakam teaches that all poloxamers are required to be at least twice the cmc is incorrect" (Brief, page 11). In response, Examiner never states or concludes that "generally Katakam teaches that all poloxamers are required to be at least twice the cmc". In the last Office action, page 4, Examiner stated: "The 0.01% of Poloxamer 188 is twice of cmc (0.0055%) needed for the surfactant to form a complete monolayer on the surface of micelle as taught by Katakam". Here, Examiner clearly stated that the cmc is the concentration that is needed for the surfactant to form a complete monolayer on the surface of micelle as taught by Katakam.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/ROBERT XU/

Examiner, Art Unit 1777

Conferees:

/Vickie Kim/

Supervisory Patent Examiner, Art Unit 1777

/Anthony McFarlane/